

Translational medicine: What is in a name from the perspective of Chinese clinicians?

ZENG GuangQiao & ZHONG NanShan*

State Key Laboratory of Respiratory Disease, First Affiliated Hospital of Guangzhou Medical College, Guangzhou 510120, China

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Translational medicine is an emerging medical practice that involves multidisciplinary collaborations to bridge between basic sciences and clinical use, aiming at enhancing patient care and preventive measures. As it suggests for most, basic scientists in particular, the term “translational medicine” may literally imply a uni-directional endeavor to use data or findings in basic research for development of novel therapies or medical procedures, and then test them in humans. This is not always the case, because what is found in laboratories does not fully mean what should happen in a real-world human body. More efforts need to be focused on feedback understandings of how humans react to the treatment. In fact, the one-way concept no longer suffices, and a two-way feature of translational medicine has been proposed elsewhere [1]: from bench to bedside and from bedside to bench.

Although starting late, translational medicine as an inter-disciplinary science is developing rapidly and widely in China. Sustainability of such development entails close collaboration between persons on laboratory benches and those at the bedside. Unfortunately, the paradigm between basic and clinical science has often put these two disciplines at odds with each other [2], and communications between basic and clinical scientists is rare and sporadic [3]. The ultimate goal of this science behooves us to have a better look at what translational medicine means to Chinese clinicians.

For the part of Chinese clinicians, translational medicine may be interpreted in several directions (Figure 1).

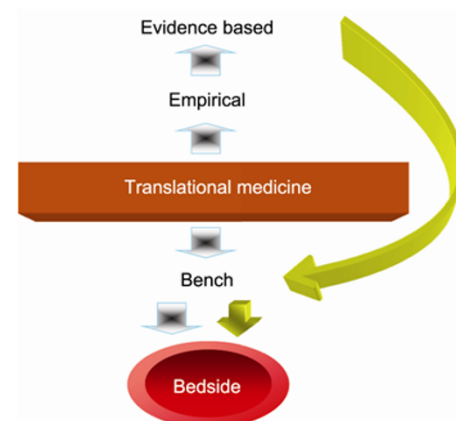


Figure 1 On the part of Chinese clinicians, the routes of translation should ideally be set as (i) from bench to bedside; (ii) from empirical to evidence based, and (iii) from bedside to bench then back to bedside.

1 From bench to bedside

“From bench to bedside” represents the traditional one-way modality of translational medicine, in which, clinicians are recipients of overwhelming data surging out of the basic science community. Since China is a developing country with a large population of patients but very limited financial resources, our clinicians need to translate laboratory findings into simpler, cheaper and effective products or measures with less adverse effects for purposes of clinical diagnosis and management.

This rationale can be well illustrated with our previous

*Corresponding author (email: nanshan@vip.163.com)

study on chronic obstructive pulmonary disease (COPD). COPD, one of the most common chronic respiratory diseases in China, is a pathological process involving oxidative stress that contributes substantially to inflammation in the airway [4–7]. *In vitro* study has shown that thiol compounds (e.g., N-acetyl-carbocysteine) are selective scavenger of reactive intermediates [8]. Mo *et al.* [9,10] also demonstrated that thiol compounds exhibit strong antioxidative properties by inhibiting activation of transcription factor (e.g., NF- κ B) and cytokine release (IL-6, IL-8), inhibiting lipid peroxidase (LPO) and enhancing antioxidant levels (serum glutathione) in smoking rat COPD models.

Based on these preliminary results, along with much more from certain suboptimally-designed clinical trials, we conducted a randomized, double-blind, parallel-group, and placebo-controlled multicenter study (Preventive Effect on Acute exacerbation of COPD with Carbocisteine (PEACE study)). Compared with placebo, the use of carbocisteine for one year was associated with a 24.5% reduction in frequency of COPD exacerbation (1.35 vs. 1.01 episodes per patient-year), improved quality of life as measured by St George's Respiratory Questionnaire (SGRQ) and no apparent adverse effects, although the lung function did not show any significant change from baseline in either of the two arms [11]. Importantly, carbocisteine showed satisfactory efficacy in reducing exacerbation rate of COPD comparable with inhaled corticosteroids plus long-acting β -agonists (ICS+LABA) or Tiotropine, and was more affordable (only one-sixth of the medical costs with standard treatments) and more simple to be used (oral administration) [11]. This study was rated later as "paper of the year 2008" by Lancet's Editorial Board [12]. In an accompanying editorial, Albert and Calverley commented that the PEACE study has "offered a cost-effective and well-tolerated way of lessening the burden of exacerbations for the growing number of patients in developing countries affected by this chronic and debilitating condition" [13].

2 From empirical to evidence-based practicing

Traditional Chinese medicine (TCM) is a broad set of healing theories and practices whose practitioners trace its origins to ancient Chinese texts dating back over 2000 years. TCM is currently not only widely practiced among Chinese, but also increasingly popular among non-Chinese in many countries. The use of treatment methods and herbal formulas in TCM remains largely empirical, and therefore the management and outcomes may vary from case to case. In an era of modern biomedicine, TCM has been constantly criticized for settling for a low standard of evidence. Some professionals stressed the dire need for evidenced-based practicing of TCM, in order to enhance patient care and promote the scientific reputation of TCM worldwide [14]. Moving TCM from empirical to evidence-based practicing

can be another important interpretation of translational medicine among Chinese clinicians.

In ancient China, management of diseases depended on the doctors' experiences. For example, patients with influenza were commonly treated with decoctions of certain herbal formula, such as weeping forsythia, heartleaf houttuynia herb and honeysuckle flower. During the 2009/2010 outbreak of swine flu, a randomized, double-blind clinical trial of those natural herbal medicine (in the form of a commercially available product, Lianhua Qingwen capsule (LHC)) was conducted in 244 patients [15], with oseltamivir as the active control. Compared with the control, LHC yielded similar therapeutic efficacy in ameliorating illness and viral shedding duration, suggesting that LHC might be used as an alternative therapeutic agent for H1N1 infection.

Chinese medicine is a great treasure to China and the world. In essence, the empirically-practicing aspect of TCM may reflect a clinical result-based pathway. In this process, what works consistently is kept, what does not is discarded, and thereby the entire system has been refined over centuries. Yet in the old times without pooled data from large-scale clinical observational studies, such a bedside-to-bedside refinement seems not efficient and convincing. Nowadays more and more well-designed clinical studies are on-going for evaluating the clinical efficacy of certain Chinese herbs, although they have been in widespread use among Chinese. We believe that evidence-based TCM in the future should owe much to our new vision of translational medicine today, and would contribute to better treatment for patients, a highly respected position of its own alongside biomedicine, or a new integrated medicine for best practices.

3 From bedside to bench to bedside

From a clinical perspective, prioritized topics for laboratory research should be those originating from clinical practices. Laboratory research should be focused on hot topics with greatest clinical relevance, and the subsequent findings can then be used immediately to make a difference in clinical practices. This strategy has shown benefits in more than one story.

3.1 Use of artemisinin in management of malaria

Earliest description of anti-malarial effects of *Artemisia annua* in China was written by Ge Hong (284–364 AD, Eastern Jin Dynasty) in a medical text called "A Handbook of Prescriptions for Emergency Treatments" (circa 340 AD). In China, a crude extract of *Artemisia annua* has been used for over 2000 years. In 1971, a collaborating team led by Tu Youyou rediscovered this anti-malarial activity; later, a purer crystalline extract named artemisinin was found, which showed strong actions against plasmodium, in partic-

ular, the plasmodium falciparum [16]. Further efforts by Tu *et al.* resulted in development of a novel compound (reduced type of artemisinin), which was 10 times more powerful than artemisinin [17]. Ever since, the compound has been modified and used worldwide. In a report of WHO Technical Consultation on Antimalarial Combination Therapy held in Geneva, Switzerland on 4–5 April, 2001, the advantages of artemisinin-based combination chemotherapy was well-documented [18]. The merits of artemisinin were also demonstrated by a medical team in a one-year fast elimination of malaria by source eradication project on Moheli Island of Comoros [19]. Owing to her great contribution in combating malaria, Prof. Tu YouYou was conferred the Lasker Award on 23 September, 2011.

3.2 Use of arsenic in management of leukemia

Although a notorious poison, arsenic is also one of the oldest drugs in both western medicine and traditional Chinese medicine, since it was mentioned by Hippocrates (462–370 BC) for treatment of skin ulcer and by the Chinese Yellow Emperor's Neijing (circa 263 BC) for treatment of malaria-associated periodic fever. In the late 18th and early 19th centuries, arsenic, in the form of Fowler's Solution (potassium bicarbonate-based solution of arsenic), was introduced in clinics to treat periodic fever, chronic myelogenous leukemia and many other diseases. In march 1971, pharmacists at the First Affiliated Hospital of Harbin Medical University developed a product called "Ai-ling No. 1" (also 713) based on a widespread empirical remedy, which contained 1 mg arsenic trioxide and 0.01 mg mL⁻¹ mercury chloride. The solution was used to treat patients with acute myeloid leukemia. Surprisingly, the remission rate was 86.3% (26.27% with complete remission) after a 4-week intravenous administration [20]. Being inspired by this clinical experience, Wang Z Y and Chen Z had further focused on the mechanism of arsenic trioxide in the management of acute promyelocytic leukemia (AML-M3) where there was an abnormal fusion gene (promyelocytic leukemia/retinoic acid receptor alpha fusion gene, or PML-RAR alpha fusion gene) arising from translocation between chromosomes 15 and 17. As₂O₃ inactivated the small ubiquitin-related modifier protein which was located on the PML-RAR alpha fusion gene. In combination with the RAR agonist all-trans retinoic acid, As₂O₃ was used in majority of patients with acute promyelocytic leukemia, yielding a 5-year survival of >90% [21].

This wonderful translation between bedside and bench has changed acute promyelocytic leukemia from highly fatal to highly curable [22].

3.3 Artificial infection with malaria parasites linked to anti-lung cancer therapy

In collaborating with epidemiologists and using the WHO cancer mortality database, Chen *et al.* carried out a longitu-

dinal analysis looking at the incidence of malaria and the mortality of lung cancer in 29 countries from 1990 to 2006. In inverse growth and decline relationship between lung cancer mortality and malaria was found overall and in some individual countries (such as Russia, Thailand, Guatemala and Tajikistan), as indicated by decreasing lung cancer rates in conjunction with increasing malaria incidence, and vice versa [23].

With this relationship in mind, we had conducted a series of studies to find out if malaria parasite infection is therapeutic for lung cancer by using both subcutaneously and intravenously implanted murine Lewis lung cancer (LLC) model. It was found that malaria infection inhibited LLC growth and metastasis and prolonged the survival of tumor-bearing mice by inducing both a potent anti-tumor innate immune response, including the secretion of IFN-gamma and TNF-alpha and the activation of NK cells. Meanwhile, tumor-bearing mice infected with the parasite developed long-lasting and effective tumor specific immunity. Furthermore, malaria parasite infection enhanced the immune response of lung cancer DNA vaccine (pcDNA 3-hMUC1) and the combination produced a synergistic anti-tumor effect. These data suggested that the malaria parasite may provide a novel strategy or therapeutic vaccine vector for anti-lung cancer immune-based therapy [23].

4 Conclusion

Translational medicine targets at bridging between basic science and clinical practice. Understanding what it means may enable the Chinese clinicians to play an active role in this field. As clinicians, we need to be keen in tackling bedside problems on the bench, but never to be lost in the laboratory. A reasonable interpretation of translational medicine will provide us assistance in diagnosis and management of human diseases.

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